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(54) Title: COMPRESSIBLE ENZYME POWDER

(57) Abstract

This invention relates to a directly compressible enzyme powder produced by mixing a liquid enzyme preparation with a suitable carrier, using the principle of wet granulation, whereby the step of freeze-drying and spray-drying is avoided. The resulting enzyme powder has extraordinary good compression qualities and may directly be tabletted.

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COMPRESSIBLE ENZYME POWDER

FIELD OF INVENTION

This invention relates to a directly compressible enzyme powder useful for producing enzyme-containing tablets. It also relates to a process for the preparation of such a powder and to a tablet prepared from such a powder.

BACKGROUND OF THE INVENTION

In the art of tablet technology tablets are often made from a spray-dried powder containing an active component which after spray-drying and prior to tabletting is mixed with one or more components (for example flow-aids) needed for tabletting to take place. Flow-aids are added in order to make the powder for tabletting free-flowing. Free-flowing means that the powder may be poured through a hopper without caking or sticking to the side walls. An example of a typical flow-aid is fumed silicon dioxide.

By using this traditional method the spray-dried powder is normally very dusty and difficult to handle, so there are safety problems by handling them if the active component has an allergy potential. Often this very dusty powder also has to be handled in more than one operation: First the spray-dried powder is mixed with flow-aids as described above, and then a granulation may be needed in order to give the powder the right strength for tabletting.

To overcome these difficulties much effort has been put into developing directly compressible powders which are non-dusting and free-flowing, for instance by spray-drying an emulsion containing a vitamin, a carbohydrate and a gelatin (see US 4,892,889).

Tablets containing enzymes such as amylases, proteases, lipases, invertases, papain, trypsin, pepsin, pancreatin, etc. have been described long ago (see for instance US

3 515 642). They are made by the conventional methods of converting a freeze-dried or spray-dried powder into tablets.

SUMMARY OF THE INVENTION

In accordance with this invention, it has surprisingly been found that a directly compressible enzyme powder may be produced by mixing a liquid enzyme preparation with a suitable carrier, using the principle of wet granulation, whereby the step of freeze-drying and spray-drying is avoided. The resulting enzyme powder has extraordinary good compression qualities and may directly be tabletted.

Accordingly, in a first aspect the present invention relates to a directly compressible powder, which comprises a carbohydrate and an enzyme. In a second aspect the invention relates to a process for the preparation of such a powder and to a tablet prepared from such a powder.

DETAILED DISCLOSURE OF THE INVENTION

Directly Compressible Powders

According to this invention the directly compressible powder comprises a carrier of carbohydrate(s) and one or more enzymes.

In the present context a directly compressible powder is a powder which may be directly tabletted without adding any excipients except possibly a lubricant. This means that no flow-aids and binders are added before tabletting, but a lubricant such as stearic acid, hydrogenated vegetable oil or Mg stearate may be added, if necessary.

In order to make the powder directly compressible the demands made on the carrier are quite large: It has to be a material with plastic properties (so that the resulting tablet does not fall apart before use), on the other hand, when the tablet is used the carrier must be able to absorb liquid and make the tablet disintegrate. Moreover, as the powder is directly compressible, the powder should be free-flowing, which

means that no flow-aids need to be added before tabletting. Lastly, as the resulting tablet may be ingested by humans, the carrier should preferably be non-toxic.

In order to make the powder directly compressible the water content of the powder may be of at the most 10%(w/w), preferably in the range of 3-5%(w/w), and the particles of the powder may be in the range from 50 to 1500 μm, preferably in the range from 125 to 1000 μm, more preferably in the range from 150 to 700 μm.

Some carbohydrates or mixtures of carbohydrates posses the above mentioned properties of workable carriers. It has especially been found that starch, sugar and sugar alcohols or any mixtures thereof may give very good carriers. For instance, the starch may be maize starch, potato starch, rice starch, wheat starch, in fact any starch of vegetable origin. The sugar may be any mono-, di- or oligosaccharide, e.g. sucrose, maltose, lactose, galactose, fructose or glucose. The sugar alcohol may be any alcohol of a mono-, di- or trisaccharide, e.g. sorbitol, mannitol or xylitol. All these carbohydrates are available from normal commercial sources.

It has been found that a superior carrier consists of a mixture of maize starch and sorbitol. The maize starch is preferably present in an amount of 65-90%(w/w), while the sorbitol is preferably present in an amount of 10-35%(w/w), more preferably the maize starch is present in an amount of 75%(w/w) and the sorbitol in an amount of 25%(w/w).

Enzymes

According to the invention, the enzyme could be any enzyme, e.g. one which may be used in the preparation of food and feed, a medicinal enzyme, an enzyme used for digestive aids, an enzyme useful for technical applications or any application where a precise and safe dosage of an enzyme is needed or desirable. The enzyme may be chosen from oxidoreductases such as peroxidases and glucoseoxidases, hydrolases such as carbohydrases (e.g. amylases, hemicellulases, cellulases, inulinases, lactases and galactosidases), proteases

(e.g. serin proteases and aspartic proteases), lipases and phytases, isomerases such as glucoseisomerases or any mixture thereof. The enzyme may be of microbial, plant or animal origin. The enzyme may be a recombinant enzyme or an enzyme recovered from its natural source.

The enzyme is added to the carrier as a liquid enzyme preparation. The liquid enzyme preparation may be an enzyme concentrate. An enzyme concentrate is produced by removing the production strain from the fermentation broth, for example by filtration or centrifugation, whereafter the liquid is concentrated to the desired enzyme strength, for example by ultrafiltration or by evaporation. The enzyme concentrate may be stabilized by preservatives such as sorbate or benzoate and/or by stabilizers such as polyols (e.g. propylene glycol), boric acid, salts, sugar (e.g. glucose and sucrose) or sugar alcohols (e.g. sorbitol) or carbohydrates of low molecular weight. pH may be adjusted and stabilized, for instance with buffer salts such as salts from organic acids, e.g. sodium citrate and sodium lactate.

It has been found that α-galactosidase concentrate derivable from Aspergillus, in particular from A. niger or A. aculeatus (having an enzyme activity of 250-100000 GALU/g, preferably an activity of 1000-25000 GALU/g, more preferably an activity of 2000-5000 GALU/g) is a very suitable enzyme concentrate.

1 GALU is the unit of α-galactosidase strength. It is defined as the amount of α-galactosidase required to form 1 μmole of p-nitro phenol + galactose from p-nitrophenyl α-D-galactopyranoside in one minute under standard conditions of pH 5.5 at 37°C. The procedure is further described below.

It has also been found that lactase concentrate (having an enzyme activity of 250-100000 LAU/g, preferably 1000-25000LAU/g, more preferably an activity of 2000-8000 LAU/g) is a very suitable enzyme concentrate.

1 LAU is the unit of lactase strength. It is defined as the amount of lactase required to release 1 μmole of glucose per minute from a solution of 4.75% w/v lactose in M-buffer pH

6.5 at 37°C. M-buffer is a special buffer designed to give the same major mineral concentrations as found naturally in cow's milk. M-buffer contains:

Na_3citrate X $2H_2O$:	2.70 mMoles/litre
Citric acid X $2H_2O$:	7.91 mMoles/litre
K_2SO_4:	1.03 mMoles/litre
K_2HPO_4:	2.99 mMoles/litre
KH_2PO_4:	10.80 mMoles/litre
KOH:	19.43 mMoles/litre
$MgCl_2$ X $6H_2O$:	4.08 mMoles/litre
$CaCl_2$ X $2H_2O$:	5.10 mMoles/litre
4 N NaOH solution:	10.00 mMoles/litre
$NaHCO_3$:	3.33 mMoles/litre.

Granulation

In the process of the invention the powder may be made in accordance with well-known procedures of making wet granulation, for instance by using a convective mixer, preferably a high shear mixer, more preferably a high shear, high speed mixer, followed by fluid bed drying, optionally followed by a sieving. According to the invention it is preferred to use a high shear, high speed mixer of the trade mark "Fielder", "Lödige", "Diosna" or "Rowenta". High shear, high speed mixers from "Fielder", "Lödige" and "Diosna" are well known. A "Rowenta" consists of a sphere-shaped granulation chamber in which the carrier is mixed by means of a fast rotating knife, and the liquid enzyme preparation is poured into the unit from the top. The mixing is continued until the carrier is evenly wetted and a proper granulate has been formed. Accordingly, it will be understood that the term "powder" is also intended to include granulates. In accordance with this invention the directly compressible powder may contain no lubricants, or a lubricant may be added to the carbohydrate(s) before granulation (preferred), or a lubricant may be added during the granulation, or a lubricant may be added at a separate mixing after the granulation and before the tabletting. The lubricant may be

added in an amount of at the most 20%(w/w), preferably in an amount of 0.25-10%(w/w).

According to the invention it is preferred to make a wet granulation consisting of a liquid enzyme preparation and a carrier, but the wet granulation may also consist of a carrier mixed with a spray-dried or freeze-dried enzyme powder whereto a liquid is added. The great disadvantage by using a spray-dried or freeze-dried enzyme powder is the dust problem described above.

In order to make a non-dusty powder the size of the particles is preferably at least 50 μm. On the other hand, they may also be too large to be directly compressible. It has been found that the particles of the powder may be in the range from 50-1500μm, preferably in the range from 125-1000μm, more preferably in the range from 150-700μm.

It is important that the powder has the right water content in order to make it directly compressible. The water content is measured by loss on drying. A water content of at the most 10%(w/w), preferably a water content of 3-5%(w/w), may be accomplished by using any method known in the art, an example of which is conventional fluid-bed drying. The temperature of the fluid-bed should be adjusted to a level which does not deactivate the enzyme(s).

After fluid-bed drying the powder may be sieved, whereafter it is ready for tabletting.

Potential Applications

The directly compressible enzyme powder described in this invention may be used in all circumstances where a precise and safe dosage of an enzyme is needed or desired, for instance in dairies where a milk clotting enzyme may be added as tablets, or in the digestive aid industry for various digestive enzyme tablets, or in technical applications, for instance for washing, dish-washing and denim-washing purposes.

In particular for use as digestive aids, the tablets may be provided with an enteric coating to protect the enzyme(s) from degradation by gastric fluid. Examples of suitable

enteric coating agents are cellulose acetate phthalate (CAP, Cellacephate®), vinyl acetate crotonic acid copolymer (Luviset®), methacrylic acid, (meth)acrylic acid ester copolymer (Eudragit®) or hydroxypropyl methylcellulose phthalate. For a further description of enteric coatings and coating processes, reference is made to WO 87/07292.

Manual Method For Determination of α-Galactosidase Activity

Reagents:

1. BUFFER: Acetate buffer 0.05 M, pH 5.5

A: 11.55 ml of glacial acetic acid p.a. are dissolved in demineralized water. Make up to 1000 ml.

B: Dissolve 16.4 g of sodium acetate, p.a. in demineralized water and make up to 1000 ml.

Buffer: Mix 7.5 ml of A and 42.5 ml of B and make up to 200 ml with demineralized water.

Max. advisable storage time: 1 month at 25°C.

2. SUBSTRATE: 1.2 mM p-Nitrophenyl-α-D-galactopyranoside

Dissolve 0.0383 g of p-Nitrophenyl-α-D-galactopyranoside · 1 H_2O (Pierce N-0877) in acetate buffer 0.05 M and make up to 100 ml.

Max. advisable storage time: 1 week at 4°C.

3. STOP REAGENT: Borax - NaOH buffer 0.0625 M, pH 9.7

Dissolve 47.63 g of $Na_2B_4O_7$ · 10 H_2O in 500 ml of slightly heated demineralized water. Cool and transfer to a 2000 ml volumetric flask. Add demineralized water to approximate 1500 ml. Add 20 ml of 4 N NaOH. Adjust pH to 9.7 with 4 N NaOH and make up to the 200 ml mark with demineralized water.

Max. advisable storage time: 2 months at 25°C.

4. COLOUR STANDARD: 4-Nitrophenol, 240 μM

A: Dissolve 0.0334 g of 4-Nitrophenol (Merck 820896) in demineralized water. Make up to 1000 ml. 4 Nitrophenol should be handled in a well-ventilated room.

Make a standard curve as follows:

I	240 μM:	A used undiluted
II	160 μM:	100 ml of A + 50 ml of demineralized water
III	80 μM:	50 ml of A + 100 ml of demineralized water
IV	40 μM:	25 ml of A + 125 ml of demineralized water

Max. advisable storage time: 1 month at 25°C.

Procedure:

Colour Standard

Make the colour standard values by mixing 2 ml of substrate and 1 ml of colour standard. Add 5 ml stop reagent.

When making the colour standard blank use demineralized water instead of colour standard. Measure OD_{405}.

Make standard and standard blank at room temperature.

Sample

Weigh and dilute the enzyme to a concentration corresponding to an activity of about 0.0015 GALU/ml.

	Sample	Sample blank
Sample	1 ml	1 ml
Preheat substrate for 5 minutes	37°C	
Add substrate (stop watch) and mix	2 ml	
Incubation for 15 minutes	37°C	room temp.
Add stop reagent and mix	5 ml	5 ml
Substrate - room temperature		2 ml
Measure OD_{405} within 30 minutes*		

*OD measurements should be finished within 30 minutes due to the risk of OD-change.

Calculation of Activity:

Make the colour standard curve (▲OD against concentration). The activity is calculated according to the following formula:

$$Act = \frac{(A_S - A_B) \cdot F_S \cdot 10^{-3}}{T \cdot M}$$

where

A_S = The reading on the standard curve in μM 4-NP, corresponding to OD_{405} for the sample.

A_B = The reading on the standard curve in μM 4-NP, corresponding to OD_{405} for the sample blank.

F_S = Dilution factor for the sample.

T = Reaction time in minutes (= 15).

M = Amount of sample weighed out.

10^{-3} = Conversion factor 1/ml.

The invention is further illustrated in the following examples which are not intended to be in any way limiting to the scope of the invention as claimed.

EXAMPLE 1

α-Galactosidase Powder(1)

α-Galactosidase Concentrate

α-galactosidase 1550 GALU/g
20%(w/w) sorbitol
2%(w/w) NaCl
3%(w/w) sodium citrate
0.2%(w/w) potassium sorbate

pH of the α-galactosidase concentrate was 6.0. The portion of dry matter was approximately 50%.

Wet Granulation

A powder consisting of

45 g of α-galactosidase concentrate (see above)
133 g of maize starch (CERESTAR, GLOBE 03302)
43 g of sorbitol (ROQUETTE FRERES, NEOSORB 60)

was made in a Rowenta-mixer (MULTIMIXER KA-70). This powder was dried in a fluid-bed for 20 min. at 60°C. (the temperature of the product was max. 40°C).

The dried granulate was sieved through a sieve with a mesh size of 0.7 mm.

The dried and sieved granulate was tabletted without adding any other components. The tablets had a hardness of 11-12 kp. The disintegration time of the tablets was measured to approximately 5 min. in water at 37°C (Ph. Eur.). Tablet weight was 430 mg. The punches used were 10.5 mm (diameter), normal concave.

EXAMPLE 2

α-Galactosidase Powder (2)

a-Galactosidase Concentrate

The same as described in Example 1.

Wet Granulation

A powder consisting of

45 g of α-galactosidase concentrate (see Ex. 1)
125 g of maize starch (see Ex. 1)
60 g of sorbitol (see Ex. 1)

was made in a Rowenta-mixer (see Ex. 1)

This powder was dried in a fluid-bed for 20 min. at 60°C (the temperature of the product was max. 40°C).

The dried granulate was sieved through a sieve with a mesh size of 0.7 mm.

1% Mg stearate was added to the dried and sieved granulate before tabletting. The resulting tablets had a hardness of 9-10 kp. The disintegration time of the tablets was measured to approximately 6 min. in water at 37°C (Ph.Eur.). Tablet weight was 430 mg. The punches were 10.5 mm (diameter), normal concave.

EXAMPLE 3

α-Galactosidase Powder (3)

α-Galactosidase Concentrate

α-galactosidase 3000 GALU/g

pH of the α-galactosidase-concentrate was 5.0. The portion of dry matter was approximately 48%.

Wet Granulation

A powder consisting of

45 g of α-galactosidase (described above)
133 g of maize starch (see ex.1)
43 g of sorbitol (see Ex. 1)

was made in a Rowenta-mixer (see Ex. 1).

This powder was dried in a fluid-bed for 20 min. at 60°C (the temperature of the product was max. 40°C).

The dried granulate was sieved through a sieve with a mesh size of 0.7 mm.

0.5% Mg stearate was added to the dried and sieved granulate before tabletting. The resulting tablets had a hardness of 3.5 kp. The disintegration time of the tablets was measured to < 10 min. in water at 37°C (Ph.Eur.). Tablet weight was 251 mg. The punches used were 8.0 mm (diameter), normal concave.

EXAMPLE 4

α-Galactosidase Powder (4)

α-Galactosidase Concentrate

α-Galactosidase 3930 GALU/g

pH of the concentrate was 5.0. The dry matter content approximately 48%.

Wet Granulation

A powder consisting of

24.7 g of α-Galactosidase (described above)
126.0 g of maize starch (see Ex. 1)
50.0 g of sucrose powder (DDS, Flor)
10.0 g of hydrogenated vegetable oil (Edward Mendell, Lubritab)

was made in a Rowenta-mixer (see Ex. 1).

The powder was dried in a fluid-bed for 20 min. at 60°C (the temperature of the product was max. 40°C). The dried granulate was sieved through a sieve with a mesh size of 0.7 mm.

The sieved granulate was compressed into tablets in an excenter tabletting machine. The resulting tablets had a hardness of approx. 6 kp and the disintegration time was measured to less then 10 min. in water at 37°C (Ph.Eur.). Tablet weight was 333 mg. The punches used were 9.5 mm (diameter), normal concave.

EXAMPLE 5

α-Galactosidase Powder (5)

α-Galactosidase Concentrate

α-Galactosidase 3930 GALU/g

pH of the concentrate was 5.0. The dry matter content approximately 48%.

Wet Granulation

A powder consisting of

24.7 g of α-Galactosidase (described above)
126.0 g of maize starch (see Ex. 1)
50.0 g of sorbitol (see Ex. 1)
10.0 g of hydrogenated vegetable oil
(Edward Mendell, Lubritab)

was made in a Rowenta-mixer (see Ex. 1)

The powder was dried in a fluid-bed for 20 min. at 60°C (the temperature of the product was max. 40°C). The dried granulate was sieved through a sieve with a mesh size of 0.7 mm.

The sieved granulate was compressed into tablets in an excenter tabletting machine. The resulting tablets had a hardness of approx. 6 kp, and the disintegration time was measured to less than 10 min. in water at 37°C (Ph.Eur.). Tablet weight was 333 mg. The punches used were 9.5 mm (diameter), normal concave.

EXAMPLE 6

α-Galactosidase Powder (6)

α-Galactosidase Concentrate

α-Galactosidase 3930 GALU/g

pH of the concentrate was 5.0. The dry matter content approximately 48%.

Wet Granulation

A powder consisting of

24.7 g of α-Galactosidase (described above)
126.0 g of maize starch (see Ex. 1)
50.0 g of mannitol (Roquette Freres, Standard)
10.0 g of hydrogenated vegetable oil
(Edward Mendell, Lubritab)

was made in a Rowenta-mixer (see Ex. 1).

The powder was dried in a fluid-bed for 20 min. at 60°C (the temperature of the product was max. 40°C). The dried granulate was sieved through a sieve with a mesh size of 0.7 mm.

The sieved granulate was compressed into tablets in an excenter tabletting machine. The resulting tablets had a hardness of approx. 2 kp, and the disintegration time was measured to less than 10 min. in water at 37°C (Ph.Eur.). Tablet weight was 333 mg. The punches used were 9.5 mm (diameter), normal concave.

EXAMPLE 7

α-Galactosidase Powder (7)

α-Galactosidase Concentrate

α-Galactosidase 3930 GALU/kg

pH of the concentrate was 5.0. The dry matter content approximately 48%.

Wet Granulation

A powder consisting of

24.7 g of α-Galactosidase (described above)
108.0 g of maize starch (see Ex. 1)
25.0 g of mannitol (see Ex. 6)
43.0 g of sorbitol (see Ex. 1)
10.0 g of hydrogenated vegetable oil
(Edward Mendell, Lubritab)

was made in a Rowenta-mixer (see Ex. 1).

The powder was dried in a fluid-bed for 20 min. at 60°C (the temperature of the product was max 40°C). The dried granulate was sieved through a sieve with a mesh size of 0.7 mm.

The sieved granulate was compressed into tablets in an excenter tabletting machine. The resulting tablets had a hardness of approx. 5 kp, and the disintegration time was measured to less than 10 min. in water at 37°C (Ph.Eur.). Tablet weight was 333 mg. The punches used were 9.5 mm (diameter), normal concave.

EXAMPLE 8

Lactase Powder (1)

Lactase Concentrate

Lactase 6400 LAU/g
32% (w/w) sorbitol
0.2% (w/w) Potassium sorbate

pH of the concentrate was 5.4. The portion of dry matter was approximately 50%.

Wet Granulation

A powder consisting of

50.0 g of Lactase Concentrate (described above)
126.0 g maize starch (see Ex. 1)
50.0 g of sucrose powder (see Ex. 4)
10.0 g of hydrogenated vegetable oil (Edward Mendell, Lubritab)

was made in a Rowenta-mixer (see Ex. 1).

The powder was dried in a fluid-bed for 20 min. at 60°C (the temperature of the product was max. 40°C). The dried granulate was sieved through a sieve with a mesh size of 0.7 mm.

The sieved granulate was compressed into tablets in an excenter tabletting machine. The resulting tablets had a hardness of approx. 6-8 kp, and the disintegration time was

measured to less than 10 min. in water at 37°C (Ph.Eur.). Tablet weight was 333 mg. The punches used were 9.5 mm (diameter), normal concave.

EXAMPLE 9

Lactase Powder (2)

Lactase Concentrate

Lactase 4500 LAU/g

The dry matter was approximately 52%.

Wet Granulation

A powder consisting of

50.0 g of Lactase Concentrate (described above)
126.0 g of maize starch (see Ex. 1)
50.0 g of sucrose powder (see Ex. 4)
10.0 g of hydrogenated vegetable oil
(Edward Mendell, Lubritab)

was made in a Rowenta-mixer (see Ex. 1)

The powder was dried in a fluid-bed for 20 min. at 60°C (the temperature of the product was max. 40°C). The dried granulate was sieved through a sieve with a mesh size of 0.7 mm.

The sieved granulate was compressed into tablets in an excenter tabletting machine. The resulting tablets had a hardness of approx. 6-8 kp, and the disintegration time was measured to less than 10 min. in water at 37°C (Ph.Eur.). Tablet weight was 400 mg. The punches used were 9.5 mm (diameter), normal concave.

CLAIMS

1. A directly compressible powder, which comprises a carbohydrate and an enzyme.

2. A powder according to claim 1, wherein the powder is free-flowing.

3. A powder according to claims 1 or 2, in which the particles of the powder are in the range from 50 to 1500 μm, preferably in the range from 125 to 1000 μm, more preferably in the range from 150 to 700 μm.

4. A powder according to any of claims 1-3, characterized by having a water content of at the most 10%(w/w), preferably a water content in the range of 3-5%(w/w), measured by loss on drying.

5. A powder according to claim 1, wherein the carbohydrate is a starch, or the carbohydrate is a sugar, or the carbohydrate is a sugar alcohol, or the carbohydrate is a mixture of a sugar and a sugar alcohol, or the carbohydrate is a mixture of a starch and a sugar and/or a sugar alcohol.

6. A powder according to claim 5, wherein the starch is of vegetable origin.

7. A powder according to claim 5 or 6, wherein the starch is maize starch, potato starch, rice starch or wheat starch.

8. A powder according to claim 7, wherein the starch is maize starch.

9. A powder according to claim 5, wherein the said sugar is a mono-, di- or oligosaccharide, and the said sugar alcohol is an alcohol of a mono-, di- or trisaccharide.

10. A powder according to claim 9, wherein the sugar is sucrose, maltose, lactose, galactose, fructose or glucose, and the sugar alcohol is sorbitol, mannitol or xylitol.

11. A powder according to claim 10, wherein the sugar alcohol is sorbitol.

12. A powder according to any of claims 5-11, wherein the carbohydrate is a mixture of 65-90%(w/w) maize starch and 10-35%(w/w) sorbitol.

13. A powder according to any of claims 1-12, wherein the enzyme is a microbial enzyme or an enzyme of animal or plant origin.

14. A powder according to claim 13, wherein the enzyme is a mixture of two or more enzymes.

15. A powder according to claim 13 or 14, wherein the enzyme is an enzyme useful for the preparation of food and feed, a medicinal enzyme, an enzyme useful for digestive aids or an enzyme useful for technical applications.

16. A powder according to any of claims 13-15, wherein the enzyme is an oxido-reductase, a hydrolase, an isomerase or any mixture thereof.

17. A powder according to any of claims 13-16, wherein the enzyme is an α-galactosidase.

18. A powder according to claim 17, wherein the enzyme is an α-galactosidase derivable from Aspergillus, in particular from A. niger or A. aculeatus.

19. A powder according to claims 17 or 18, wherein the α-galactosidase has an activity of 50-20000 GALU/g,

preferably an activity of 200-5000 GALU/g, more preferably an activity of 400-1000 GALU/g.

20. A process for producing a powder according to any of claims 1-19, comprising mixing a liquid enzyme preparation with a carbohydrate in a convective mixer, subjecting the resulting mixture to drying and optional sieving so as to obtain a powder having a particle size in the range from 50 to 1500 μm, preferably in the range from 125 to 1000 μm, more preferably in the range from 150 to 700 μm.

21. A process according to claim 20, wherein the convective mixer is a high shear mixer, preferably a high shear, high speed mixer.

22. A process according to claim 20, wherein the carbohydrate is a starch, or the carbohydrate is a sugar, or the carbohydrate is a sugar alcohol, or the carbohydrate is a mixture of a sugar and a sugar alcohol, or the carbohydrate is a mixture of a starch and a sugar and/or a sugar alcohol.

23. A process according to claim 22, wherein the starch is of vegetable origin.

24. A process according to claim 22 or 23, wherein the starch is maize starch, potato starch, rice starch or wheat starch.

25. A process according to claim 24, wherein the starch is maize starch.

26. A process according to claim 22, wherein the said sugar is a mono-, di- or oligosaccharide, and the said sugar alcohol is an alcohol of a mono-, di- or trisaccharide.

27. A powder according to claim 26, wherein the sugar is sucrose, maltose, lactose, galactose, fructose or glucose, and the sugar alcohol is sorbitol, mannitol or xylitol.

28. A process according to claim 27, wherein the sugar alcohol is sorbitol.

29. A process according to any of claims 20-28, wherein the carbohydrate is a mixture of 65-90%(w/w) maize starch and 10-35%(w/w) sorbitol.

30. A process according to claim 20, wherein the enzyme is a microbial enzyme or an enzyme of animal or plant origin.

31. A process according to claim 30, wherein the enzyme is a mixture of two or more enzymes.

32. A process according to claim 30 or 31, wherein the enzyme is an enzyme useful for the preparation of food and feed, a medicinal enzyme, an enzyme useful for digestive aids or an enzyme useful for technical applications.

33. A process according to any of claims 30-32, wherein the enzyme is an oxidoreductase, a hydrolase, an isomerase or any mixture thereof.

34. A process according to any of claims 30-33, wherein the enzyme is an α-galactosidase.

35. A process according claim 34, wherein the enzyme is an α-galactosidase derivable from Aspergillus, in particular from A. niger or A. aculeatus.

36. A process according to claim 34 or 35, wherein the liquid α-galactosidase preparation has an activity of 250-

100000 GALU/g, preferably 1000-25000 GALU/g, more preferably 2000-5000 GALU/g.

37. A process according to any of claims 20-36, wherein the carbohydrate is a mixture of maize starch and sorbitol, and the enzyme is a liquid α-galactosidase preparation.

38. A tablet prepared from the powder according to any of claims 1-19.

39. A process of preparing an enzyme-containing tablet comprising mixing a liquid enzyme preparation with one or more carbohydrate(s), subjecting the resulting mixture to drying and optional sieving so as to obtain a powder having a particle size in the range from 50 to 1500 μm, preferably in the range from 125 to 1000 μm, more preferably in the range from 150 to 700 μm, and subjecting the resulting powder directly to tabletting.

40. A process according to claim 39, wherein a lubricant in an amount of at the most 20%(w/w), preferably in an amount of 0.25-10%(w/w), is added to the carbohydrate(s) before mixing with the liquid enzyme preparation.

41. A process according to claim 39, wherein a lubricant in an amount of at the most 20%(w/w), preferably in an amount of 0.25-10%(w/w), is added during mixing.

42. A process according to claim 39, wherein a lubricant in an amount of at the most 20%(w/w), preferably in an amount of 0.25-10%(w/w), is added after mixing, drying and sieving.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 94/00237

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 9/16, C11D 3/386, A23K 1/165, A23L 1/30
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C12N, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dialog Information Services, file 351, DERWENT WPI, Dialog accession no. 008934442/7, WPI accession no. 92-061711/08, (AMAN) AMANO PHARM KK: "Easily breakable tablet prepn. useful as detergent - by adding water-sol. binder and wetting agent to enzyme, mixed and then incorporating breaking agent and lubricant to granule", & JP 4008288 A 920113 9208 (Basic)	1-42
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X	DE, A, 2140747 (E.I. DU PONT DE NEMOURS AND CO.), 17 February 1972 (17.02.72)	1-42
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 1994	11.10.94
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 94/00237

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dialog Information Services, file 351, DERWENT WPI, Dialog accession no. 003941331/7, WPI accession no. 84-086875/14, (ANTI=) ANTIBIOTICS RES: "Prepn. of enzyme tablets by pressing uses casein, starch, lactose or soluble starch as stabiliser and drying by lyophilic or spray method", & SU 1024087 A 830623 8414 (Basic) --	1-16,38-42
X	Patent Abstracts of Japan, Vol 12,No 155, C-494, abstract of JP, A, 62-269685 (SHOWA DENKO K.K.), 24 November 1987 (24.11.87) -- --------	1-37

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/08/94

International application No.
PCT/DK 94/00237

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		FR-A- 2104349	14/04/72
		GB-A- 1316522	09/05/73
		NL-A- 7111106	16/02/72
		SE-B,C- 395221	08/08/77
		US-A- 3721725	20/03/73
		US-A- 3928566	23/12/75
		US-A- 3932943	20/01/76